REMARKS

Upon entry of this amendment, claims 1, 5, 41 and 46 are pending in the instant application. Claims 2-4 are cancelled without disclaimer of the subject matter. New claims 63 and 64 have been added. Applicants reserve the right to pursue this subject matter in a later application.

Amendments to claims 1, 5, 41 and 46 were made to more particularly point out the claimed subject matter, and to correct antecedent bases. Support for claim 1 amendments appears in claim 1 as originally filed. Support for claim 5 amendments appears in the specification at least, *e.g.*, at page 26, lines 3-14, and at page 27, lines 5-18, Examples 9 and 10, and in Figures 16-18. Support for amendments to claim 46 appears at least, *e.g.*, in claim 41 as originally filed. Support for new claims 63 and 64 appears at least, *e.g.*, in claim 1 as originally filed, and in the specification at least, *e.g.*, at page 11, lines 16-20. No new matter has been added.

Claims have been objected to and rejected on various grounds. Each will be addressed in turn below.

Claim Objections

Claim 2, 5 and 46 have been objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 2 has been cancelled. Claim 5 has been amended to place it in proper dependent form. Claim 46 has been amended to place in proper dependent form and to particularly point out multiple elements of the kit. Withdrawal of these objections is hereby requested.

Claim Rejections

Examiner's Position

In the Office Action dated April 17, 2002, the Examiner made the following rejections:

(1) 35 U.S.C. §101 - Claims 1-5, 41 and 46 were rejected as not supported by a specific, substantial, or credible utility.

(2) 35 U.S.C. §112, first paragraph - Claims 1-5, 41 and 46 were rejected for failing to adequately enable one skilled in the art to use the claimed invention.

(3) 35 U.S.C. §112, first paragraph - Claims 1-5, 41 and 46 were rejected for lack of written description.

(4) 35 U.S.C. §112, second paragraph - Claim 5 was rejected for being indefinite.

(5) 35 U.S.C. §102(b) - Claims 1-2, 5, 41 and 46 were rejected for being anticipated.

Applicants traverse each of these rejections as applied to the claims as amended and address each individually as follows.

The § 101 rejections are overcome; Combined §§ 101, 112 rejections are overcome

Claims 1-5, 41 and 46 have been rejected under 35 U.S.C. § 101 alone, and under the combination of 35 U.S.C. § 101 and 35 U.S.C. §112 paragraph 1, as not being supported by either a specific, substantial and credible asserted utility or a well-established utility. According to the Examiner, "the instant application does not disclose the biological role of the nucleic acid, the encoded protein or the significance of either." (Office Action at p. 4). The Examiner further characterizes these claims as failing to adequately teach how to use the instant invention. (Office Action at page 9). Claims 2-4 have been canceled. Applicants traverse these rejections on the remaining claims for the reasons described below.

Specific, substantial and credible utility for the claimed FGF-CX polypeptide (SEQ ID NO:2; *see*, FIG. 1), FGF-CX nucleotide (SEQ ID NO:1; *see*, FIG. 1) and anti FGF-CX antibody is provided throughout the specification. Specific examples of utility include:

- FGF-CX polypeptide has 70-80 % identity and 81-89% positive homology to FGF family members FGF-9 and XFGF-CX. *See, e.g.*, FIGS. 4 - 9.
- FGF-CX residues aa 125-148 have 100% identity to the conserved FGF family domain. *See, e.g.*, page 91, lines 3-6, FIG. 13 double underlined. (alignment repeated below).

```
Motif:        G.L.G.....EC.F.E.....Y
FGF-CX  125   GELYGSEKLTSECIFREQFEENWY   148
```

- FGF-CX residues aa 95-120 contain the FGF internal hydrophobic transport domain. *See, e.g.*, page16 lines 13-16.
- FGF-CX polypeptide shares the FGF family's functional characteristic of binding heparin sulfate proteoglycan (HSPG) present on the surface of cells and in the extracellular matrix (ECM). *See, e.g.*, Example 7.

- FGF-CX protein demonstrates functional growth factor-like activity *in vitro* in various fibroblast cell lines. *See, e.g.*, Examples 9 and 10, FIG. 16. *See*, also, page 102, line 28-29.

- FGF-CX polypeptide demonstrates functional growth factor activity *in vivo*. *See, e.g.*, Example 11.

The polypeptides of the present invention were initially characterized as members of the FGF family of proteins based on homology. The Utility Examination Guidelines state that "when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the Examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Fed. Reg., Vol. 66. No. 4, January 5, 2001, p. 1096. The elected polypeptide of the invention is fully characterized as a fibroblast growth factor (FGF). The well-established utility for FGF family of proteins include growth, survival, apoptosis, motility and differentiation, as given in Page 8, lines 20-22 of the instant specification. As shown in Examples 9 - 11, Applicants have presented the data showing that the protein of the present invention facilitates cell growth in NIH 3T3 mouse fibroblasts, human cell lines CCD-1070Sk normal human skin fibroblasts and CCD-1106 keratinocytes (Figure 16 in the instant specification). Furthermore, Applicants present the data wherein NIH 3T3 cells cultured with FGF protein showed 3-fold increase in cell number as compared to the control (Figure 17 in the instant specification), demonstrating a role in cell proliferation. Applicants disclosure of FGF-CX's role in cell growth and proliferation is thus fully supported by experimental evidence, and is a credible, substantial and specific utility. FGF-CX's biological activity is aptly demonstrated and disclosed in the specification.

The Examiner has rejected the proliferation data based on the fact that the cells lose contact inhibition and thus may take on a transformed phenotype. The Applicants traverse the rejection. FGFs are known to modulate the shape and motility of many cell types, due in part to FGF-induced changes in integrin expression and disassembly of the actin stress-fiber cytoskeleton. Morphological changes observed in cells treated with FGF-CX are identical to that shown in the literature with FGF-2 treatment. For example, NIH 3T3 cells treated with FGF-CX demonstrate migratory behavior, whereupon they become spindly and refractile. *See*, Example 10. Likewise, smooth muscle cells treated with FGF-2 acquired a distinct spindle-like shape within 24 hours. *See*, Pickering *et al.*, *Circ. Res.* 1997, 80:627-637 (Form 1449/PTO ref. C15).

In addition, FGF has been shown to promote migratory behavior in NIH 3T3 cells. See, Bikfalvi *et al.*, *J. Cell Biol.* 1995, 129:233-243 (Form 1449/PTO ref. C16). Since FGF alters the integrin expression, the disorganized pattern and loss of contact is inherent with the treatment of FGF. Thus Applicants point out that morphological transformation of cells is known to accompany proliferation that is well documented in the prior art.

The Examiner statement that the disclosed protein "only shares approximately 70% amino acid sequence similarity/identity with the most closely related protein of the prior art" is moot. As noted above, the polypeptide of the present invention is a member of the FGF family of proteins based on demonstrated functional activity, homology, and domain characterization. Although the FGF family is diverse and complex according to Galzie *et al.* (provided by the Examiner), Galzie *et al.* does not discuss or mention the protein of the instant invention. Galzie *et al.* thus cannot support a case for lack of utility of the present invention.

Consistent with the teachings of the specification, and with the utilities known by those of ordinary skill in the art, Applicants respectfully submit that it is clear that the FGF-CX nucleic acids and the encoding polypeptide of the present invention can be used diagnosing proliferative disorders, and have a demonstrated ability to stimulate the growth of cells (pg. 77, lines 18-22; Examples 9-10), and thus has credible, specific and substantial utilities. FGF-CX has utility in screening for and identifying specific cancers. *See, e.g.*, specification at page 75, lines 11-24. As described in Example 8 and shown in FIG. 15, FGF-CX expression correlates directly with the presence or absence of cancer in specific tissues. FGF-CX expression in normal lung, liver, colon, breast and uterus is normally low, but increases significantly in cancers of the same tissue (FIG. 15, Panels A-C). Likewise, FGF-CX expression is high in normal bladder, but is low to undetectable in bladder cancer (FIG. 15, Panel C). Thus, determining the presence or absence of FGF-CX in these listed tissues has specific, substantial and credible utility that directly correlates with diagnosing a particular disease.

Accordingly, Applicants submit that the claimed invention has a utility that is credible, substantial and specific, and is fully characterized in the instant disclosure of the invention. Applicants therefore respectfully request withdrawal of the rejection based on 35 U.S.C. §101, either alone or in combination with 35 U.S.C. §112, paragraph 1.

The § 112, first paragraph rejections are overcome

Utility-Based Rejections are overcome

Claims 1, 5, 41 and 46 have been rejected under 35 U.S.C. § 112, first paragraph, because the Examiner states that one skilled in the art would not know how to use an invention that lacks utility. Applicants traverse this rejection. As described above, claims 1, 5, 41 and 46 do have a specific, substantial, and credible utility as a novel fibroblast growth factor and a diagnostic for specific diseases. Because the claims have such utility, Applicants submit that they are fully enabled. Thus, the rejection of these claims should be withdrawn.

Written Description-Based Rejections are overcome

Claims 1, 5, 41 and 46 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Claims 2-4 have been cancelled and thus are not under consideration. Claims 1 and 5 have been amended in such a way that they no longer recite polypeptides having at least 85% identity to SEQ ID NO:2, or a variant form of a mature form of an amino acid sequence, as requested by the Examiner. The mature FGF-CX is rewritten into new claims 63 and 64, in order to more particularly point out the embodiment where the amino acid sequence of SEQ ID NO:2 comprises a post-translational modifications other than a proteolytic cleavage. Modifications other than proteolytic cleavage are disclosed in the specification as including, by way of non-limiting example, "myristoylation or phosphorylation." See page 11, lines 16-19. It would be routine to one skilled in the art at the time of the invention to analyze the elected polypeptide for consensus phosphorylation, myristylation sites. An example analysis of the FGF-CX polypeptide using the PROSITE protein domain matching software is provided as Exhibit 3. Consensus sites were located for phosphorylation by protein kinase C, casein kinase II and tyrosine kinase. Additional consensus sites include those for N-myristoylation and amidation. (*See*, Exhibit 1). The presence of the FGF domain was also confirmed. Accordingly, Applicants believe that these rejections do not apply to the claims as amended and request that such rejections be withdrawn.

The § 112, second paragraph, rejection is overcome

Claim 5 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants traverse the rejection as applied to the claim as amended.

The Examiner states that recitation of "conservative substitution" in Claim 5 is unclear. Amended claim 5 now requires that a conservative amino acid substitution be made within the context of the full length SEQ ID NO:2, without altering the functional activity of the FGF polypeptide, such that the polypeptide retains its growth factor-like properties, retains the conserved amino acids of the FGF family motif, and retains the FGF hydrophobic transport domain. Thus, Applicants respectfully request that the rejection be withdrawn.

The §102(b) rejections are overcome

Claims 1-2, 5, 41 and 46 have been rejected as being anticipated by Nauro *et al.* (U.S. Pat. No. 5,512,460) ("Nauro"). Claim 2 has been cancelled to expedite prosecution. Claims 5, 41 and 46 depend from these claim 1. Applicants traverse the rejection as applied to the claims as amended.

The sequence cited on page 16 of the Office Action as prior art is Nauro SEQ ID NO:11. However, this sequence is a polynucleotide. The sequence elected in the present invention is a polypeptide. The USPTO characterizes proteins and nucleic acids as distinct inventions. *See, e.g.*, Restriction Requirement in instant invention, paper no. 7, dated December 7, 2001. Instead, Applicants will assume that the Office Action on page16 should properly recite the Nauro polypeptide sequence of SEQ ID NO:1, disclosing a 142 aa polypeptide fragment.

A ClustalW alignment of Nauro SEQ ID NO:1 and the claimed FGF-CX polypeptide of SEQ ID NO:2 is shown below. The hydrophobic transport region is marked with a tilde ("~") and the conserved amino acid residues of the FGF family motif are marked with asterisks ("*").

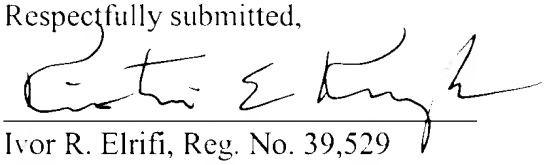
```
                        10        20        30        40        50        60
                ....|....|....|....|....|....|....|....|....|....|....|....|
Nauro SEQ:1     ------------------------------------------------------LDHL    4
FGFCX SEQ:2     MAPLAEVGGFLGGLEGLGQQVGSHFLLPPAGERPPLLGERRSAAERSARGGPGAAQLAHL   60

                        70        80        90       100       110       120
                ....|....|....|....|....|....|....|....|....|....|....|....|
Nauro SEQ:1     HGILRRRQLYCRTGFHLEIFPNGTIQGTRKDHSRFGILEFISIAVGLVSIRGVDSGLYLG   64
FGFCX SEQ:2     HGILRRRQLYCRTGFHLQILPDGSVQGTRQDHSLFGILEFISVAVGLVSIRGVDSGLYLG  120
                                                  ~~~~~~~~~~~~~~~~~~~~~~~~~~~

                       130       140       150       160       170       180
                ....|....|....|....|....|....|....|....|....|....|....|....|
Nauro SEQ:1     MNEKGELYGSEKLTQECVFREQFEENWYNTYSSNLYKHVDTGRRYYVALNKDGTPREGTR  124
FGFCX SEQ:2     MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR  180
                  * * *     ** * *       *

                       190       200       210
                ....|....|....|....|....|.
Nauro SEQ:1     TKRHQKFTHFLPRPVDPD----------    142
FGFCX SEQ:2     SKRHQKFTHFLPRPVDPERVPELYKDLLMYT  211
```

Amended claims 1 and 5 no longer recite "variant" or "a variant polypeptide." Thus these claims cannot be anticipated by the amino acid molecule of Nauro *et al.* As amended, all claims require a full length polypeptide that has the C-terminal and N-terminal portions not present in Nauro SEQ ID NO:1. Claims 1, 5, 41 and 46 are no longer anticipated by Nauro *et al.*, and Applicants request that the Examiner withdraw all §102(b) rejections.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance, and request an action be issued to this effect. With the accompanying Petition for a Three Month Extension of Time and fee, these documents are due on or before October 17, 2002. The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 15966-557 CIP (Cura-57 CIP). If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



Ivor R. Elrifi, Reg. No. 39,529
Kristin E. Konzak, Reg. No. 44,848
Attorney/Agent for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS
GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

Dated: October 7, 2002

Please address all correspondence to Customer Number 30623.

30623
PATENT TRADEMARK OFFICE

Appendix A: Version Marked to Show Changes Made in Abstract

In the specification:

Amend the Abstract on page 81 as indicated below.

The present invention provides FGF-CX [, a novel isolated polypeptide, as well as a polynucleotide encoding FGF-CX] polypeptides and polynucleotides, and antibodies that immunospecifically bind to FGF-CX or any derivative, variant, mutant, or fragment of the FGF-CX polypeptide, polynucleotide or antibody. The invention additionally provides methods [in which] of use for the FGF-CX polypeptide, polynucleotide and antibody[are used in detection and treatment of a broad range of pathological states, as well as to other uses].

Replace page 115 with substitute page 115, attached hereto.

Appendix B: Version Marked to Show Changes Made in Claims

In the claims:

Cancel claims 2, 3 and 4 without prejudice and without disclaimer of the subject matter.

Amend claims 1, 5 and 46 as indicated below.

1. (Amended) An isolated polypeptide comprising an amino acid sequence [selected from the group consisting of:

a) an amino acid sequence given by] shown in SEQ ID NO:2 [;

b) a variant of an amino acid sequence given by SEQ ID NO:2, in which any amino acid specified in the chosen sequence is changed to a different amino acid, provided that no more than 15% of the amino acid residues in the sequence are so changed;

c) a mature form of an amino acid sequence given by SEQ ID NO:2; and

d) a variant of a mature form of an amino acid sequence given by SEQ ID NO:2, wherein any amino acid in the mature form of the chosen sequence is changed to a different amino acid, provided that no more than 15% of the amino acid residues in the sequence of the mature form are so changed; and

e) a fragment of an amino acid sequence described in paragraphs a) to d)].

5. (Amended) The polypeptide of claim 1, [wherein said polypeptide is a variant polypeptide, and wherein one or more of any amino acid specified in SEQ ID NO:2 is changed to provide a conservative substitution] said polypeptide further comprising at least one conservative amino acid substitution, wherein said polypeptide is a full length polypeptide that retains functional growth factor-like properties of SEQ ID NO: 2, retains the conserved amino acids of the FGF family motif located at residues 125, 127, 129, 136, 137, 139, 141 and 148, and retains the hydrophobic transport domain between residues 92-120, wherein the residues are numbered with respect to SEQ ID NO:2.

41. (Amended) A [pharmaceutical] composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.

46. (Amended) A kit comprising in one or more containers a [pharmaceutical] composition [of claim 41] comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.

Add the following new claims:

-- 63. The polypeptide of claim 1, the polypeptide further comprising a post-translational modification other than a proteolytic cleavage.

64. The polypeptide of claim 63, wherein the post-translational modification is at least one modification chosen from the group consisting of phosphorylation and N-myristoylation. --

Exhibit 1

PROSITE software Domain Analysis

PROSITE - Protein Domain Matches for Gene ID: FGF20X

```
Pattern-ID: PKC_PHOSPHO_SITE PS00005 (Interpro) PDOC00005
Pattern-DE: Protein kinase C phosphorylation site
Pattern:    [ST].[RK]
   47       SAR
   109      SIR
   130      SEK
   161      TGR
   174      TPR
   181      SKR

Pattern-ID: CK2_PHOSPHO_SITE PS00006 (Interpro) PDOC00006
Pattern-DE: Casein kinase II phosphorylation site
Pattern:    [ST].{2}[DE]
   42       SAAE
   88       TRQD
   174      TPRD

Pattern-ID: TYR_PHOSPHO_SITE PS00007 (Interpro) PDOC00007
Pattern-DE: Tyrosine kinase phosphorylation site
Pattern:    [RK].{2,3}[DE].{2,3}Y
   111      RGVDSGLY
   140      REQFEENWY

Pattern-ID: MYRISTYL PS00008 (Interpro) PDOC00008
Pattern-DE: N-myristoylation site
Pattern:    G[^EDRKHPFYW].{2}[STAGCN][^P]
   8        GGFLGG
   18       GQQVGS
   50       GGPGAA
   83       GSVQGT
   112      GVDSGL

Pattern-ID: AMIDATION PS00009 (Interpro) PDOC00009
Pattern-DE: Amidation site
Pattern:    .G[RK][RK]
   161      TGRR

Pattern-ID: HBGF_FGF PS00247 (Interpro) PDOC00220
Pattern-DE: HBGF/FGF family signature
Pattern:    G.[LIM].[STAGP].{6,7}[DE]C.[FLM].E.{6}Y
   125      GELYGSEKLTSECIFREQFEENWY
```